TECHNICAL BRIEF SERIES:
MATERIAL SCIENCE FOR NITROSAMINE MITIGATION

REDUCING NITRITE LEVELS IN EXCIPIENTS WITH ACTIVE MATERIAL SCIENCE TECHNOLOGY

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Introduction

The safety and efficacy of pharmaceutical drugs is paramount in ensuring public health. However, an emerging concern has drawn significant attention within the pharmaceutical industry and regulatory agencies worldwide – the presence of nitrosamines in pharmaceutical products. Nitrosamines are a class of organic compounds known for their potential carcinogenicity, which has prompted rigorous investigations into their formation, detection, and mitigation.

The International Agency for Research on Cancer (IARC) classified nitrosamines into four groups, based on their carcinogenic potential [1]. Group 1 compounds, e.g., N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NMK), have sufficient incidences of carcinogenic effects on humans while group 2A compounds N-nitrosodimethylamine (NDMA), N-nitrosodiethylamine (NDEA), etc., are probably carcinogenic to humans with limited evidence in humans but sufficient evidence in animals. Group 2B compounds, such as 1-methyl-4-nitrosopiperazine (NMP), are considered possibly carcinogenic to humans with limited evidence in humans and animals. Finally, group 3 compounds, such as N-nitrosodiphenylamine are nitrosamines with inadequate data on their carcinogenicity in humans and experimental animals [1,2].

Nitrosamines are usually formed through nitrosation reactions, where amines react with nitrite, often arising from the reaction between secondary or tertiary amines and nitrosating agents (nitrous acid, etc.) [2-4]. Studies show that environmental factors can cause nitrosamine levels in packaging to increase over the FDA's set daily allowable intake limit. Nitrite impurities are common and can lead to the formation of N-nitroso API impurities (nitrosamines) in the drug product during manufacturing and/or shelf life of the drug product.

Since 2018, there have been numerous recalls of drugs due to the presence of nitrosamines. The issue first gained widespread attention with the recall of blood pressure medications such as valsartan and losartan, which were found to contain nitrosamines like N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA). This was followed by recalls of other

IDEA IN BRIEF

THE PROBLEM

Pharma companies are currently working against a ticking clock to reformulate drugs to mitigate nitrosamine risk to meet new regulatory requirements and deadlines. Commonly used excipients with high nitrite impurity levels can be a key source of nitrosamine formation.

THE CHALLENGE

Current mitigation strategies employed by pharma developers, such as changes to their formulation or manufacturing processes can be costly and time consuming. In order to meet impending deadlines, additional or alternative mitigation strategies, such as packaging changes, need to be considered to fully address risk and expedite implementation of a solution.

THE SOLUTION

New innovations in active material science technologies offer an active packaging based solution that can mitigate risk without reformulation. This technology scavenges, reacts with, and/or adsorbs/absorbs nitrosamine precursors in the packaging headspace to deliver a meaningful reduction in nitrite impurity levels found in excipients, inhibiting Nitrosamine formation and helping pharma companies achieve regulatory compliance within the required timeframes.

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medications, including the heartburn drug ranitidine (Zantac), the diabetes medication metformin, and the smoking cessation drug Chantix.

The discovery of nitrosamine impurities in pharmaceuticals sparked a comprehensive evaluation of various drug classes and their potential susceptibility to nitrosamine formation. Regulatory authorities such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) swiftly issued guidelines and regulations mandating rigorous testing and acceptable limits for nitrosamine impurities in pharmaceuticals (see Figure 1) [5-6].

Nitrosamine	AI Limit (ng/day)
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5

Figure 1: AI Limits of the most common nitrosamines in drug products.

In response to this challenge, the pharmaceutical industry, with the help of packaging industry, has been diligently working to identify and implement strategies to prevent, detect, and mitigate nitrosamine impurities in drug formulations. This paper navigates the complex landscape of nitrosamines in pharmaceuticals, shedding light on the challenges and solutions proposed by Aptar CSP Technologies. It explores the different N-Sorb solutions for mitigating nitrosamines or nitrosating agents, highlighting the critical factors.

Introduction to the N-Sorb Technology Platform

Different raw active materials that can mitigate nitrosating agents were engineered for inclusion into a polymer matrix (Activ-Polymer™ technology platform) to form N-Sorb technology, which mitigates N-nitrosamine formation by scavenging nitrosating agents. Figure 2 illustrates Activ-Polymer™ technology, which employs active materials as fillers in composite materials to improve their physical and/or adsorption/absorption properties. The proprietary technology is delivered in a unique formulation comprised of a base majority polymer that provides the physical structure, a channeling agent, and active particles. It can adsorb, absorb, and/or react with volatile gases/impurities within a sealed internal headspace of a primary or secondary packaging configuration containing oral solid dosage tablets or capsules.

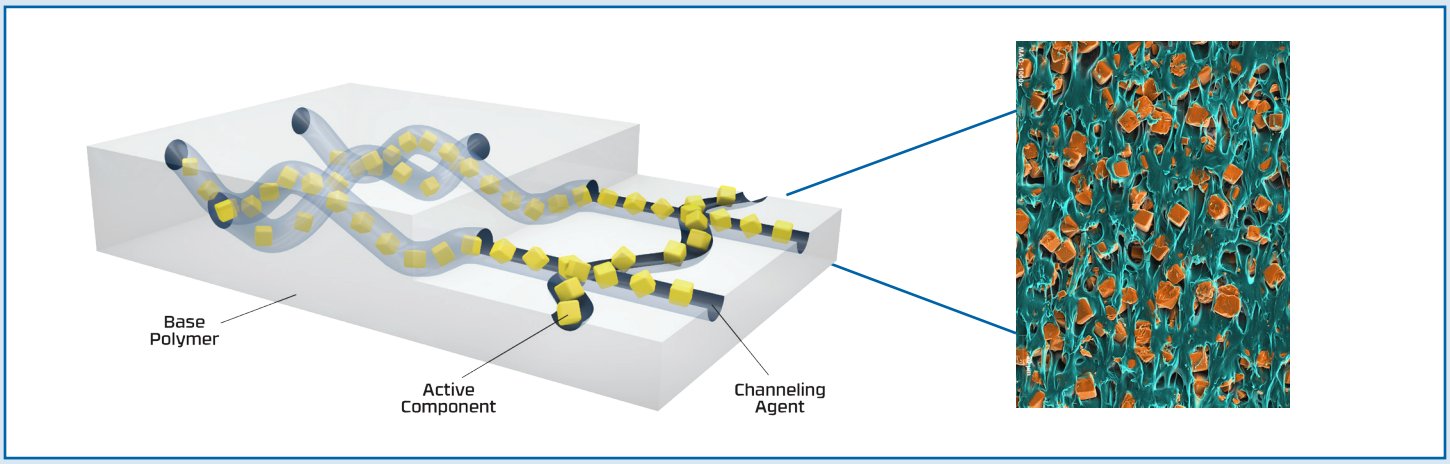

Figure 2: Representation of Activ-Polymer™ technology (left); High-resolution scanning electron microscopy image coupled with EDX analyses of an Activ-Polymer™ film (right)

Specifics on Microcrystalline Cellulose

Microcrystalline Cellulose (MCC) is primarily utilized as a diluent in all types of oral solid dosage forms, particularly tablets and capsules. The proportion of MCC can be high – up to 90% w/w of total formulation. Nitrites are major reactive impurities found in MCC. Nitrite impurities are common and can lead to the formation of N-nitroso API impurities (nitrosamines) in the drug product during manufacturing and/or shelf life of the drug product.

Method for Analysis

MCC placebo tablets manufactured by MOD3 Pharma (66 wt.% of MCC, 33 wt.% of lactose, 1% wt.% of magnesium stearate) were put in contact with N-Sorb film (1x2 inches) in aluminum foil bags (2x3 inches). These foil bags were then sealed. Control samples consisted of MCC tablets placed alone (without N-Sorb film) in aluminum foil bags. The prepared bags were then placed at different temperatures/conditions. Samples were then tested via Greiss reaction on LC-UV/VIS, LOQ = 0.1 ppm at different times to determine the remaining nitrite content in the MCC tablets. Three samples were analyzed for each time point.

Results and Discussion

Three versions of N-Sorb mitigation films were exposed to MCC tablets in sealed foil bags for up to 180 days to determine the levels of nitrite present in the samples compared to the controls.

After 7 days of aging at 25°C, all samples exposed to N-Sorb showed an overall reduction in nitrite. N-Sorb B was observed to have significant nitrite reduction, greater than 53% at 7 days. Similar trends were observed at 21 and 90 days. After 180 days of exposure, MCC tablets in contact with N-Sorb B showed the lowest nitrite content of 0.297±0.012 ppm, calculated to be a 78% reduction in nitrite compared to the control. N-Sorb B is followed in performance by N-Sorb A, with a nitrite content of 0.454±0.075 ppm and continuing to trend downward.

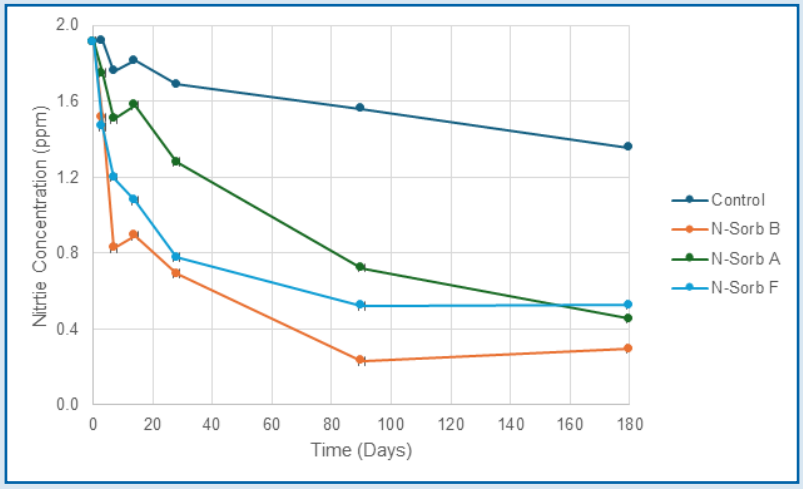

Figure 3: Evolution of nitrite concentration in MCC tablets at 25°C as a function of time in the absence or the presence of N-Sorb films.

Conclusion

N-Sorb technology in pharmaceutical packaging presents a promising strategy to mitigate the formation of nitrosamine(s) by scavenging and/or reacting with nitrosating agents in excipients, specifically nitrite. By acting as effective mitigation for nitrite, these films significantly reduce the risk of nitrosamine contamination, thereby enhancing the safety profile of the drug. The study's findings demonstrate that N-Sorb technology can reduce nitrite levels in MCC placebo tablets within a package without the need for drug reformulation which can be both costly and time consuming. This solution can empower pharmaceutical developers with an expedited solution for mitigating nitrosamine risk, helping them achieve regulatory compliance before the upcoming deadlines.

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